## REMARKS

Claims 1-8 are pending in this application. Claims 9-13 are cancelled without prejudice.

As a preliminary matter, the Office Action repeatedly refers to SEQ ID NO: 1 as a limitation of the present claims. Applicants assume that this is a typographical error in the Office Action, since the present claims refer to SEQ ID NO: 2, not to SEQ ID NO: 1. The arguments presented below are made on the assumption that all references to SEQ ID NO: 1 were intended to refer to SEQ ID NO: 2.

**All of the Present Claims are Entitled to an August 14, 1998 Priority Date.**

The Office Action indicated that an English language translation of the German priority application and a declaration under Rule 132 could be used to overcome rejections based on the Zabel *et al.* reference. Submitted herewith is a certified English translation of the German priority Application DE 198 37 015.6. The text of the translated priority application is substantially the same as the text of the present application. Accordingly, all of the present claims are amply supported by the priority application and are entitled to a priority date of August 14, 1998.

The "Declaration Under 37 CFR 132" by inventor Ulrike Zabel, submitted herewith states that Dr. Zabel is a coinventor of the invention described in the present application, along with Harald Schmidt and Wolfgang Poller. Dr. Zabel further states that she and Harald Schmidt were coauthors of Zabel *et al.*, along with Monica Wagner and Mylinh La. As attested in the Declaration, Monica Wagner was an assistant who worked under the direction of Dr. Zabel and Mylinh La was a student who worked under the guidance of Dr. Schmidt. Neither Monica Wagner nor Mylinh La made an inventive contribution to the claims of the present application. Zabel *et al.* is the work of the present inventors and was published after the priority date of the present application. Accordingly, Zabel *et al.* is not available as a reference against the present claims.

**Claims 1 and 2 Are Not Anticipated by the Applied References.**

Claim 1 has been rejected as allegedly being anticipated by Giuili *et al.* This rejection is unwarranted and should be withdrawn. Claim 1 is directed to an isolated human guanylyl cyclase $\alpha 1/\beta 1$ protein, which is an enzymatically active heterodimer comprising hsGC$\alpha$1 (having the amino acid sequence of SEQ ID NO: 2) and hsGC$\beta$1 (having the amino acid sequence of SEQ ID NO: 4). Although Giuili *et al.* purport to describe certain $\alpha$ and $\beta$

subunits of human guanylyl cyclase, the reference does not describe an enzymatically active heterodimer of hsGCα1 (SEQ ID NO: 2) and hsGCβ1 (SEQ ID NO: 4). In fact, the sequence for the α chain reported by the reference (see Fig. 2 of Giuili *et al.*) is not the same sequence as SEQ ID NO: 2 of the present application. The amino acid sequence for the α chain in Fig. 2 of Giuili *et al.* includes 717 amino acid residues, whereas SEQ ID NO: 2 includes only 690 residues. Thus, the protein structure reported by Giuili, *et al.* is not the same as the isolated protein of the present claims. Sequence in Fig. 2 of Giuili *et al.* includes a number of specific sequence differences from SEQ ID NO: 2 beginning with amino acid residue 124 and continuing through the end of the sequence. Accordingly, Giuili *et al.* does not teach or suggest the isolated human guanylyl cyclase α1/β1 protein that is presently claimed.

The specific sequence differences between SEQ ID NO: 2 and the Giuili *et al.* sequence are also highlighted in Gencore sequence matching printout for "Result 1"included with the Office Action. In this printout the differences between the database sequence and the Giuili *et al.* sequence are listed as "CONFLICTS". The sequence in the database clearly is NOT the same sequence as reported by Giuili *et al.* in Fig. 2. Furthermore, Giuili *et al.* isolated and sequenced a DNA molecule, not a protein. The present claims are directed to an isolated protein. Clearly, Giuili *et al.* does not disclose an isolated protein having the amino acid residue sequence of SEQ ID NO: 2, and thus, does not disclose all of the limitations of claim 1. Accordingly, Giuili *et al.* cannot anticipate claim 1 of the present application.

The Gencore printout bearing a date of July 2, 2003 also shows that the database sequence, for which the Examiner obtained a 100% match with SEQ ID NO: 2, was modified on May 30, 2000, which is after the priority date of the present application. Thus, this database sequence cannot be used as a reference against the present application. A copy of the Genecore printout with the relevant portions underlined, and a copy of page 85 of Giuili *et al.* with the sequence differences underlined, are attached hereto as Appendix I and Appendix II, respectively, for the convenience of the Examiner.

Claim 1 and 2 were also rejected as being anticipated by Zabel *et al.* Since Zabel *et al.* is not available as a reference against this application , this ground for rejection is moot.

**Claims 3-8 Are Not Obvious Over the Applied References.**

Claims 3-8 have been rejected as purportedly being obvious over either Zabel *et al.* or Giuili *et al.* and further in view of common knowledge in the art regarding methods of affinity chromatography using affinity tags for protein purification. This rejection is also

unwarranted, and is hereby traversed. As noted above, Zabel *et al.* is not available as a reference against the present application. Giuili *et al.* does not teach or suggest an isolated protein having the amino acid residue sequence of SEQ ID NO: 2 as explained hereinabove, which is a material limitation of all of the claims. Accordingly, even assuming common knowledge regarding purification using affinity tags, the combination of Giuili *et al.* with such common knowledge cannot and does not render claims 3-8 obvious. The issue here is not purification, but rather whether or not the claimed isolated protein would have been obvious to one of ordinary skill in the art. A *prima facie* case for obviousness has not been established. The obviousness rejection cannot stand.

**Conclusion.**

All of the present claims are deemed to be patentable over Giuili *et al.* Reconsideration and entry of this amendment are earnestly solicited. In the event that the foregoing is not deemed persuasive, Applicants request that this amendment be entered to place the application in better form for appeal.

Respectfully submitted,

Dated August 2, 2004

By _____
Talivaldis Cepuritis (Reg. No. 20,818)

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20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180

APPENDIX I

Pages 1 and 2 of Gencore Search Report labeled "us-09-762-767a-2.rsp" (provided with the Office Action), with underlining added by Applicants to point out significant information in the report relating differences between the database sequence and the sequence of Giuili *et al.*

GenCore version 5.1.6


OM protein - protein search, using sw model

Run on: June 27, 2003, 12:55:07 ; Search time 11.0695 Seconds
(without alignments)
2585.358 Million cell updates/sec

Title: US-09-762-767A-2
Perfect score: 3593
Sequence: 1 MFCTKLKDLKITGECPFSLL.....QKKDVEDGNANFLGKASGID 690

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 112892 seqs, 41476328 residues

Total number of hits satisfying chosen parameters: 112892

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : SwissProt_40:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

| Result No. | Score | % Query Match | Length | DB | ID | Description |
|---|---|---|---|---|---|---|
| 1 | 3593 | 100.0 | 690 | 1 | CYG3_HUMAN | Q02108 homo sapien |
| 2 | 3232 | 90.0 | 690 | 1 | CYG3_RAT | P19686 rattus norv |
| 3 | 3107.5 | 86.5 | 691 | 1 | CYG3_BOVIN | P19687 bos taurus |
| 4 | 1651 | 46.0 | 730 | 1 | CYG4_RAT | Q9wvi4 rattus norv |
| 5 | 1635 | 45.5 | 732 | 1 | CYG4_HUMAN | P33402 homo sapien |
| 6 | 976.5 | 27.2 | 683 | 1 | CYGH_DROME | Q07093 drosophila |
| 7 | 795 | 22.1 | 619 | 1 | CYG1_RAT | P20595 rattus norv |
| 8 | 793.5 | 22.1 | 619 | 1 | CYG1_BOVIN | P16068 bos taurus |
| 9 | 789.5 | 22.0 | 619 | 1 | CYG1_HUMAN | Q02153 homo sapien |
| 10 | 774.5 | 21.6 | 682 | 1 | CYG2_RAT | P22717 rattus norv |
| 11 | 708 | 19.7 | 617 | 1 | CYG2_HUMAN | O75343 homo sapien |
| 12 | 460 | 12.8 | 1047 | 1 | ANPB_BOVIN | P46197 bos taurus |
| 13 | 460 | 12.8 | 1047 | 1 | ANPB_HUMAN | P20594 homo sapien |
| 14 | 460 | 12.8 | 1047 | 1 | ANPB_RAT | P16067 rattus norv |
| 15 | 457.5 | 12.7 | 1057 | 1 | ANPA_RAT | P18910 rattus norv |
| 16 | 456.5 | 12.7 | 1061 | 1 | ANPA_HUMAN | P16066 homo sapien |
| 17 | 454.5 | 12.6 | 1057 | 1 | ANPA_MOUSE | P18293 mus musculu |
| 18 | 452 | 12.6 | 433 | 1 | KSGC_RAT | P55205 rattus norv |
| 19 | 450 | 12.5 | 1108 | 1 | CYGE_MOUSE | P52785 mus musculu |
| 20 | 448 | 12.5 | 1108 | 1 | CYGE_RAT | P51840 rattus norv |
| 21 | 445 | 12.4 | 1109 | 1 | CYGD_CANFA | O19179 canis famil |
| 22 | 442 | 12.3 | 1108 | 1 | CYGF_HUMAN | P51841 homo sapien |
| 23 | 440 | 12.2 | 1103 | 1 | CYGF_BOVIN | O02740 bos taurus |
| 24 | 438 | 12.2 | 1108 | 1 | CYGF_RAT | P51842 rattus norv |
| 25 | 438 | 12.2 | 1110 | 1 | CYGD_BOVIN | P55203 bos taurus |
| 26 | 434 | 12.1 | 1103 | 1 | CYGD_HUMAN | Q02846 homo sapien |
| 27 | 430 | 12.0 | 1110 | 1 | CYGX_RAT | P51839 rattus norv |
| 28 | 428.5 | 11.9 | 1050 | 1 | ANPB_ANGJA | P55202 anguilla ja |
| 29 | 427 | 11.9 | 1125 | 1 | CYGS_STRPU | P16065 strongyloce |
| 30 | 414.5 | 11.5 | 1073 | 1 | HSER_PIG | P55204 sus scrofa |
| 31 | 408.5 | 11.4 | 1073 | 1 | HSER_HUMAN | P25092 homo sapien |
| 32 | 407.5 | 11.3 | 1072 | 1 | HSER_RAT | P23897 rattus norv |
| 33 | 399.5 | 11.1 | 1076 | 1 | HSER_CAVPO | P70106 cavia porce |
| 34 | 389 | 10.8 | 1137 | 1 | CYG1_C | Q09435 caenorhabdi |
| 35 | 322.5 | 9.0 | 887 | 1 | CYA2_H | Q08462 homo sapien |
| 36 | 322 | 9.0 | 1064 | 1 | CYA4_RAT | P26770 rattus norv |
| 37 | 319.5 | 8.9 | 1099 | 1 | CYA7_MOUSE | P51829 mus musculu |
| 38 | 319 | 8.9 | 1090 | 1 | CYA2_RAT | P26769 rattus norv |
| 39 | 316 | 8.8 | 1080 | 1 | CYA7_HUMAN | P51828 homo sapien |
| 40 | 310.5 | 8.6 | 1078 | 1 | CYA7_BOVIN | Q29450 bos taurus |
| 41 | 303.5 | 8.4 | 1144 | 1 | CYA3_HUMAN | O60266 homo sapien |
| 42 | 303 | 8.4 | 1144 | 1 | CYA3_RAT | P21932 rattus norv |
| 43 | 302 | 8.4 | 1134 | 1 | CYA1_BOVIN | P19754 bos taurus |
| 44 | 290.5 | 8.1 | 2248 | 1 | CYA1_DROME | P32870 drosophila |
| 45 | 287.5 | 8.0 | 1249 | 1 | CYA8_MOUSE | P97490 mus musculu |

ALIGNMENTS

RESULT 1
CYG3_HUMAN
ID CYG3_HUMAN STANDARD; PRT; 690 AA.
AC Q02108; O43843;
DT 01-JUL-1993 (Rel. 26, Created)
DT 30-MAY-2000 (Rel. 39, Last sequence update)
DT 16-OCT-2001 (Rel. 40, Last annotation update)
DE Guanylate cyclase soluble, alpha-1 chain (EC 4.6.1.2) (GCS-alpha-1)
DE (Soluble guanylate cyclase large subunit) (GCS-alpha-3).
GN GUCY1A1 OR GUCY1A3 OR GUC1A3 OR GUCSA3.
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
RN [1]
RP SEQUENCE FROM N.A.
RC TISSUE=Brain;
RX MEDLINE=92316204; PubMed=1352257;
RA Giuili G., Scholl U., Bulle F., Guellaeen G.;
RT "Molecular cloning of the cDNAs coding for the two subunits of
RT soluble guanylyl cyclase from human brain.";
RL FEBS Lett. 304:83-88(1992).
RN [2]
RP SEQUENCE FROM N.A.
RC TISSUE=Kidney;
RA Gansemans Y., Brouckaert P., Fiers W.;
RT "Human soluble guanylate cyclase large subunit mRNA, alpha3-like.";
RL Submitted (MAY-1996) to the EMBL/GenBank/DDBJ databases.
RN [3]
RP SEQUENCE FROM N.A.
RC TISSUE=Brain;
RX MEDLINE=98416113; PubMed=9742212;
RA Zabel U., Weeger M., La M., Schmidt H.H.;
RT "Human soluble guanylate cyclase: functional expression and revised
RT isoenzyme family.";
RL Biochem. J. 335:51-57(1998).
CC -!- CATALYTIC ACTIVITY: GTP = 3',5'-cyclic GMP + diphosphate.
CC -!- ENZYME REGULATION: ACTIVATED BY NITRIC OXIDE IN THE PRESENCE OF
CC MAGNESIUM OR MANGANESE IONS.
CC -!- SUBUNIT: HETERODIMER OF AN ALPHA AND A BETA CHAIN.
CC -!- SUBCELLULAR LOCATION: Cytoplasmic.
CC -!- MISCELLANEOUS: THERE ARE TWO TYPES OF GUANYLATE CYCLASES: SOLUBLE
CC FORMS AND MEMBRANE-ASSOCIATED RECEPTOR FORMS.
CC -!- SIMILARITY: BELONGS TO ADENYLYL CYCLASE CLASS-4/GUANYLYL CYCLASE
CC FAMILY.
CC ---

CC ---
DR EMBL; X66534; CAA47145.1; -.
DR EMBL; U58855; AAB94794.1; -.

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DR   EMBL; Y15723; CAA75738.1; -.
DR   PIR; S23098; S23098.
DR   HSSP; P19687; 1AWN.
DR   Genew; HGNC:4685; GUCY1A3.
DR   MIM; 139396; -.
DR   InterPro; IPR001054; G_cyclase.
DR   Pfam; PF00211; guanylate_cyc; 1.
DR   SMART; SM00044; CYCc; 1.
DR   PROSITE; PS00452; GUANYLATE_CYCLASES_1; 1.
DR   PROSITE; PS50125; GUANYLATE_CYCLASES_2; 1.
KW   Lyase; cGMP synthesis; Multigene family.
FT   DOMAIN      481    608       GUANYLATE CYCLASE.
FT   CONFLICT    124    127       AAGV -> QQS (IN REF. 1).
FT   CONFLICT    131    184       VIKESLGEEVFKICYEEDENILGVVGGTLKDFLNSFSTLLK
FT                                QSSHCQEAGKRGR -> LSKNLLVKRFLKYVTRKMKTSLGW
FT                                LEAPLKIFKQLQYPSETEQPLPRSRKKGQ (IN REF.
FT                                1).
FT   CONFLICT    322    322       MISSING (IN REF. 1).
FT   CONFLICT    529    535       GDAYCVA -> AMPIVWL (IN REF. 1).
FT   CONFLICT    678    690       GNANFLGKASGID -> ASQFFRQSIRNRLATYIPIYKSLG
FT                                FDSLKMCRASESTLGIVDG (IN REF. 1).
SQ   SEQUENCE   690 AA;  77452 MW;  DA1E14A5E11451CF CRC64;

  Query Match           100.0%;  Score 3593;  DB 1;  Length 690;
  Best Local Similarity  100.0%;  Pred. No. 2.7e-243;
  Matches  690;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MFCTKLKDLKITGECPFSLLAPGQVPNESSEEAAGSSESCKATVPICQDIPEKNIQESLP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MFCTKLKDLKITGECPFSLLAPGQVPNESSEEAAGSSESCKATVPICQDIPEKNIQESLP 60

Qy         61 QRKTSRSRVYLHTLAESICKLIFPEFERLNVALQRTLAKHKIKESRKSLEREDFEKTIAE 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 QRKTSRSRVYLHTLAESICKLIFPEFERLNVALQRTLAKHKIKESRKSLEREDFEKTIAE 120

Qy        121 QAVAAGVPVEVIKESLGEEVFKICYEEDENILGVVGGTLKDFLNSFSTLLKQSSHCQEAG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 QAVAAGVPVEVIKESLGEEVFKICYEEDENILGVVGGTLKDFLNSFSTLLKQSSHCQEAG 180

Qy        181 KRGRLEDASILCLDKEDDFLHVYYFFPKRTTSLILPGIIKAAAHVLYETEVEVSLMPPCF 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 KRGRLEDASILCLDKEDDFLHVYYFFPKRTTSLILPGIIKAAAHVLYETEVEVSLMPPCF 240

Qy        241 HNDCSEFVNQPYLLYSVHMKSTKPSLSPSKPQSSLVIPTSLFCKTFPFHFMFDKDMTILQ 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 HNDCSEFVNQPYLLYSVHMKSTKPSLSPSKPQSSLVIPTSLFCKTFPFHFMFDKDMTILQ 300

Qy        301 FGNGIRRLMNRRDFQGKPNFEEYFEILTPKINQTFSGIMTMLNMQFVVRVRRWDNSVKKS 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 FGNGIRRLMNRRDFQGKPNFEEYFEILTPKINQTFSGIMTMLNMQFVVRVRRWDNSVKKS 360

Qy        361 SRVMDLKGQMIYIVESSAILFLGSPCVDRLEDFTGRGLYLSDIPIHNALRDVVLIGEQAR 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 SRVMDLKGQMIYIVESSAILFLGSPCVDRLEDFTGRGLYLSDIPIHNALRDVVLIGEQAR 420

Qy        421 AQDGLKKRLGKLKATLEQAHQALEEEKKKTVDLLCSIFPCEVAQQLWQGQVVQAKKFSNV 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 AQDGLKKRLGKLKATLEQAHQALEEEKKKTVDLLCSIFPCEVAQQLWQGQVVQAKKFSNV 480

Qy        481 TMLFSDIVGFTAICSQCSPLQVITMLNALYTRFDQQCGELDVYKVETIGDAYCVAGGLHK 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 TMLFSDIVGFTAICSQCSPLQVITMLNALYTR QQCGELDVYKVETIGDAYCVAGGLHK 540

Qy        541 ESDTHAVQIALMALKMMELSDEVMSPHGEPIKMRIGLHSGSVFAGVVGVKMPRYCLFGNN 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 ESDTHAVQIALMALKMMELSDEVMSPHGEPIKMRIGLHSGSVFAGVVGVKMPRYCLFGNN 600

Qy        601 VTLANKFESCSVPRKINVSPTTYRLLKDCPGFVFTPRSREELPPNFPSEIPGICHFLDAY 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 VTLANKFESCSVPRKINVSPTTYRLLKDCPGFVFTPRSREELPPNFPSEIPGICHFLDAY 660

Qy        661 QQGTNSKPCFQKKDVEDGNANFLGKASGID 690
              |||||||||||||||||||||||||||||||

Db        661 QQGTNSKPCFQKKDVEDGNANFLGKASGID 690


RESULT 2
CYG3_RAT
ID   CYG3_RAT       STANDARD;      PRT;   690 AA.
AC   P19686;
DT   01-FEB-1991 (Rel. 17, Created)
DT   01-FEB-1991 (Rel. 17, Last sequence update)
DT   16-OCT-2001 (Rel. 40, Last annotation update)
DE   Guanylate cyclase soluble, alpha-1 chain (EC 4.6.1.2) (GCS-alpha-1)
DE   (Soluble guanylate cyclase large subunit).
GN   GUCY1A1 OR GUC1A1.
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   SEQUENCE FROM N.A., AND PARTIAL SEQUENCE.
RC   TISSUE=Lung;
RX   MEDLINE=91009100; PubMed=1698769;
RA   Nakane M., Arai K., Saheki S., Kuno T., Buechler W., Murad F.;
RT   "Molecular cloning and expression of cDNAs coding for soluble
RT   guanylate cyclase from rat lung.";
RL   J. Biol. Chem. 265:16841-16845(1990).
RN   [2]
RP   SEQUENCE FROM N.A.
RC   STRAIN=Sprague-Dawley; TISSUE=Striatum;
RX   MEDLINE=97151525; PubMed=8997507;
RA   Smigrodzki R.M., Levitt P.;
RT   "The alpha 1 subunit of soluble guanylyl cyclase is expressed
RT   prenatally in the rat brain.";
RL   Brain Res. Dev. Brain Res. 97:226-234(1996).
CC   -!- CATALYTIC ACTIVITY: GTP = 3',5'-cyclic GMP + diphosphate.
CC   -!- ENZYME REGULATION: ACTIVATED BY NITRIC OXIDE IN THE PRESENCE OF
CC       MAGNESIUM OR MANGANESE IONS.
CC   -!- SUBUNIT: HETERODIMER OF AN ALPHA AND A BETA CHAIN.
CC   -!- SUBCELLULAR LOCATION: Cytoplasmic.
CC   -!- MISCELLANEOUS: THERE ARE TWO TYPES OF GUANYLATE CYCLASES: SOLUBLE
CC       FORMS AND MEMBRANE-ASSOCIATED RECEPTOR FORMS.
CC   -!- SIMILARITY: BELONGS TO ADENYLYL CYCLASE CLASS-4/GUANYLYL CYCLASE
CC       FAMILY.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; M57405; AAA41206.1; -.
DR   EMBL; U60835; AAB17953.1; -.
DR   PIR; A38297; OYRTA1.
DR   HSSP; P19687; 1AWN.
DR   InterPro; IPR001054; G_cyclase.
DR   Pfam; PF00211; guanylate_cyc; 1.
DR   SMART; SM00044; CYCc; 1.
DR   PROSITE; PS00452; GUANYLATE_CYCLASES_1; 1.
DR   PROSITE; PS50125; GUANYLATE_CYCLASES_2; 1.
KW   Lyase; cGMP synthesis; Multigene family.
FT   DOMAIN      480    607       GUANYLATE CYCLASE.
SQ   SEQUENCE   690 AA;  77566 MW;  E4819B2CA4F86401 CRC64;

  Query Match           90.0%;  Score 3232;  DB 1;  Length 690;
  Best Local Similarity  89.1%;  Pred. No. 4.3e-218;
  Matches  616;  Conservative   39;  Mismatches   34;  Indels    2;  Gaps    2;

Qy          1 MFCTKLKDLKITGECPFSLLAPGQVPNESSEEAAGSSESCKATVPICQDIPEKNIQESLP 60
              ||| | ||||||||||||||||||||| |  || || |||||:||:| ||:  | | : | |
Db          1 MFCRKFKDLKITGECPFSLLAPGQVPTEPIEEVAGVSESCQATLPTCQEFAE-NAEGSHP 59

Qy         61 QRKTSRSRVYLHTLAESICKLIFPEFERLNVALQRTLAKHKIKESRKSLEREDFEKTIAE 120
```

APPENDIX II

Page 85 of Giuili *et al.* with portions of the sequence that differ from the Gencore database sequence underlined by Applicants.

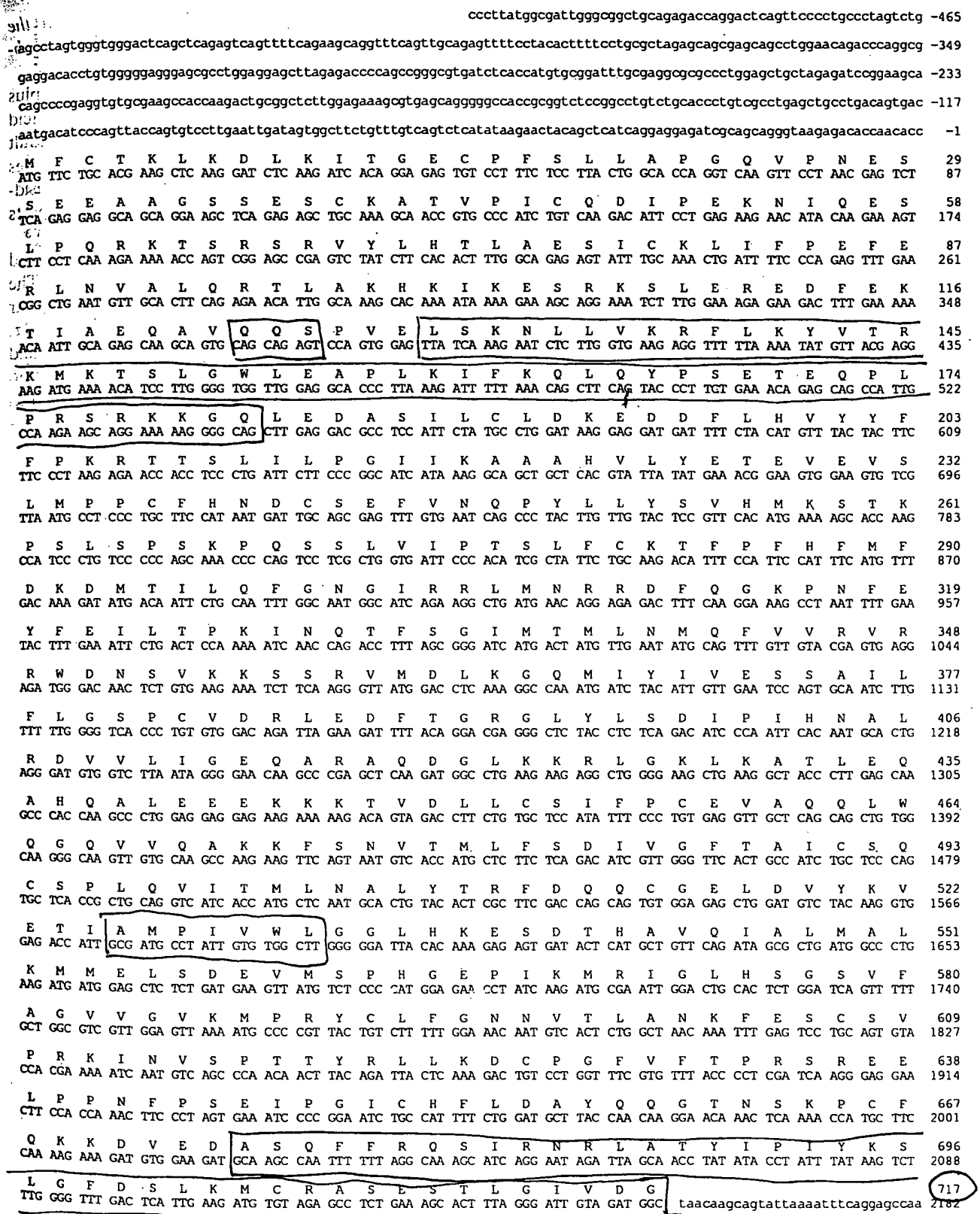


Fig. 2. Nucleotide sequence and corresponding protein sequence of GC-S$\alpha_3$.